Effect of a high protein meal on the bioavailability of verapamil

The bioavailabilities of the high-clearance drugs propranolol and metoprolol are 40% to 90% greater when these drugs are given after food. In the case of propranolol the increase in AUC correlates linearly with the protein content of the meal (Melander *et al.*, 1977; McLean *et al.*, 1981; Walle *et al.*, 1981). We have examined the possibility of a similar phenomenon occurring with verapamil since this drug, like propranolol and metoprolol, also has a high-clearance rate and a high hepatic first pass metabolism (Woodcock *et al.*, 1981a,b).

The subjects were nine healthy males between the ages 22 and 28 years who weighed 64 to 75 kg. All were non-smokers and had fasted overnight for at least 12 h. Verapamil was administered orally as a 120 mg dragee (Isopstin®, Knoll AG) immediately after (post-prandial) or 2.5 h before (fasting) a standard meal containing 34 g (22%) protein, 42 g (27%) fat and 75 g (51%) carbohydrate, equivalent to 3.6×10^3 kJ. The treatments were carried out using a randomized crossover design and were separated by an interval of at least 7 days. Subjects remained in the sitting position for 2 h after the dose since posture has been shown to influence hepatic blood flow and could therefore affect drug absorption (Daneshmend *et al.*, 1981). Blood samples (10 ml) were taken from a forearm vein at 0 h and then 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 h after administration. Serum was stored at -18°C until analysis. Verapamil serum concentrations were determined by gas chromatography using a nitrogen detector. The within-day coefficient of variation for the range 9–90 ng ml $^{-1}$ was 4–7% (Nelson *et al.*, 1979). The statistical significance of the differences were evaluated using the Wilcoxon signed rank test.

The high protein meal produced only minor changes in verapamil concentrations in contrast to the marked elevation in levels reported for propranolol and metoprolol. Indeed, the mean peak plasma concentration ($C_{\max}$) of verapamil if anything tended to be lower after food, 77 ng ml $^{-1}$, in comparison with the fasting state, 118 ng ml $^{-1}$, $P < 0.1$ (Table 1). This is an unexpected observation since our standard meal contained 34 g protein, which in the study of Walle *et al.*

Table 1 Effect of a high protein meal on the pharmacokinetic parameters of orally administered verapamil (mean $\pm$ s.d.).

	Fasting	Post-prandial	
$C_{\max}$ (ng ml $^{-1}$)	118 $\pm$ 82	77 $\pm$ 51	NS
$t_{\max}$ (h)	1.6 $\pm$ 0.7	3.1 $\pm$ 0.8	$P < 0.01$
$t_{1/2}$ (h)	4.5 $\pm$ 3.2	4.5 $\pm$ 3.9	NS
AUC (ng ml $^{-1}$ h)	428 $\pm$ 201	445 $\pm$ 319	NS

(1981), raised the AUCs of propranolol, on average, by more than 90%. The possibility that the high protein meal reduced the absorption of verapamil from the gastrointestinal tract is unlikely since a food induced reduction in absorption has not been demonstrated for other high clearance drugs such as propranolol, metoprolol, acebutolol or labetalol. Melander & McLean (1983) have suggested that the food effect on bioavailability may only occur with drugs undergoing hydroxylation and conjugation since a standardised breakfast had no effect on the bioavailability of amitriptyline and prazosin where the presystemic metabolism involves dealkylation. The primary metabolic pathways of verapamil are *N*-dealkylation and *O*-demethylation (Eichelbaum *et al.*, 1979) and thus our findings are consistent with this hypothesis. It is of interest that food was without effect on the bioavailability of the β -adrenergic receptor blocking agent acebutolol which is metabolised in the liver to a primary amine and then acetylated to diacetolol (Zaman *et al.*, 1984).

We also observed a significant prolongation in $t_{\max}$ (Table 1). This effect has been reported for other drugs, e.g. labetalol (Mäntylä *et al.*, 1980) and has been attributed to delayed gastric emptying, a phenomenon which could also account for the observed reduction in $C_{\max}$.

The AUC $_{\text{oral}}$ is an important clinical index of the effect of food on the bioavailability of drugs. This is because a change in AUC $_{\text{oral}}$ can lead to altered blood concentrations under steady-state treatment. Since this study has shown that the

AUC of verapamil is little affected by a high protein meal a modification in dosage according to eating habits does not seem necessary.

B. G. WOODCOCK, N. KRAEMER &
N. RIETBROCK

*Department of Clinical Pharmacology, University
Clinic Frankfurt, Federal Republic of Germany*

Received 26 July 1985,
accepted 2 November 1985

References

- Daneshmend, T. K., Jackson, L. & Roberts, C. J. C. (1981). Physiological and pharmacological variability in estimated hepatic blood flow in man. *Br. J. clin. Pharmac.*, **11**, 491–496.
- Eichelbaum, M., Ende, M., Remburg, G., Schomerus, M. & Dengler, H. J. (1979). The metabolism of ¹⁴C-D,L-verapamil in man. *Drug Metab. Dispos.*, **7**, 145–148.
- Mäntylä, R., Allonen, H., Kanto, J., Kleimola, T. & Sellman, R. (1980). Effect of food on the bioavailability of labetalol. *Br. J. clin. Pharmac.*, **9**, 435–437.
- McLean, A. J., Isbister, C., Bobik, A. & Dudley, F. J. (1981). Reduction of first-pass hepatic clearance of propranolol by food. *Clin. Pharmac. Ther.*, **30**, 31–34.
- Melander, A. & McLean, A. (1983). Influence of food on presystemic clearance of drugs. *Clin. Pharmacokin.*, **8**, 286–296.
- Melander, A., Danielson, K., Schersten, B. & Wahlin, E. (1977). Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin. Pharmac. Ther.*, **22**, 108–112.
- Nelson, K., Woodcock, B. G. & Kirsten, R. (1979). Improvement of the quantitative determination of verapamil in human plasma. *Int. J. clin. Pharmac. Biopharm.*, **17**, 375–379.
- Walle, T., Fagen, T. C., Walle, U. K., Oexmann, M. J., Conradi, E. C. & Gaffney, T. E. (1981). Food-induced increase in propranolol bioavailability—Relationship to protein and effects on metabolites. *Clin. Pharmac. Ther.*, **30**, 790–795.
- Woodcock, B. G., Rietbrock, I., Vöhringer, H. F. & Rietbrock, N. (1981a). Verapamil disposition in liver disease and intensive-care patients: Kinetics, Clearance, and apparent blood flow relationships. *Clin. Pharmac. Ther.*, **29**, 27–34.
- Woodcock, B. G., Schulz, W., Kober, G. & Rietbrock, N. (1981b). Direct determination of hepatic extraction of verapamil in cardiac patients. *Clin. Pharmac. Ther.*, **30**, 52–56.
- Zaman, R., Wilkins, M. R., Kendall, M. J. & Jack, D. B. (1984). The effect of food and alcohol on the pharmacokinetics of acebutolol and its metabolite, diacetolol. *Biopharm. Drug Dispos.*, **5**, 91–95.

The effect of enalapril on baroreceptor mediated reflex function in normotensive subjects

In a recent article in the Journal, Giudicelli *et al.* (1985) reported on the influence of enalapril on baroreflexes in an attempt to explain the absence of tachycardia with blood pressure reduction, a characteristic haemodynamic feature of angiotensin converting enzyme (ACE) inhibitors. Their focus was mainly on baroreceptor reflexes, hence their article somehow obscures other possible explanations for the absence of reflex cardioacceleration including (1) a central sympatho-inhibitory action, (2) removal of the peripheral angiotensin II (AII) mediated presynaptic facilitation of noradrenaline release, (3) unchanged arterial wall tangential tension during ACE inhibition, (4) selective venodilatation or (5) parasympathetic activation. The relative merits of these propositions have been examined previously (Sturani *et al.*, 1982; Ajayi *et al.*, 1985a,b; Campbell *et al.*, 1985; Levenson *et al.*, 1985).

We would like to report on our experience with chemically diverse ACE inhibitors on baroreceptor reflex function in five separate studies. In salt replete normotensive males (24 h urine sodium 120–180 mEq) aged 18–35 years, we assessed the influence of single doses of captopril (50 mg), enalapril (10 mg), a lysine analogue of enalapril, lisinopril (10 mg), cilazapril (RO-312848) 5 mg and perindopril S-9490-3, 8 mg, on the Valsalva manoeuvre, a non-invasive test of baroreceptor reflex function (Sharpey-Shafer, 1955). The studies were of a single-blind (enalapril and lisinopril) or double-blind (captopril, perindopril, cilazapril) placebo controlled, randomised crossover design. The Valsalva manoeuvre was performed in duplicate, with on line computer analysis of R-R interval changes (Ajayi *et al.*, 1985b).

The ACE inhibitors altered neither the sym-